Prognostic factors of oligometastatic non-small-cell lung cancer following radical therapy: a multicentre analysis

Opitz, Isabelle ; Patella, Miriam ; Payrard, Loic ; Perentes, Jean Yannis ; Inderbitzi, Rolf ; Gelpke, Hans ; Schulte, Sandra ; Diezi, Maja ; Gonzalez, Michel ; Krueger, Thorsten ; Weder, Walter

Abstract: OBJECTIVES Patients with oligometastatic non-small-cell lung cancer (NSCLC) may benefit from therapy with curative intent. Our goal was to identify prognostic factors related to better prognosis in a multicentre analysis of patients who underwent surgery of primary tumours in combination with radical treatment of all metastatic sites. METHODS We retrospectively reviewed the records of oligometastatic patients who underwent resection of primary tumours at 4 centres (August 2001-February 2018). Oligometastasis was defined as 5 synchronous metastases in 2 organs. Radical metastatic treatment was surgery, radiotherapy or a combination. The Cox proportional hazards model was used for identification of prognostic factors on overall survival. RESULTS We treated 124 patients; 72 (58%) were men, mean age 60 ± 9.8 years, with 87 (70%) adenocarcinoma. Sixty-seven (54%) patients had positive pathologic-N stage (pN). Brain metastases were most common (n = 76; 61%) followed by adrenal (n = 13; 10%) and bone (n = 12; 10%). Systemic therapy was administered in 101 (82%) patients. Median follow-up was 60 months [95% confidence interval (CI) 41-86]. Thirty- and 90-day mortality rates were 0 and 2.4%, respectively. One-, 2-, and 5-year overall survival were 80%, 58% and 36%, respectively. Cox regression analysis showed that patients 60 years [hazard ratio (HR) 0.41, 95% CI 0.24, 0.69; P = 0.001] and patients with pN0 (HR 0.38, 95% CI 0.21-0.69; P = 0.002) had a significant survival benefit. The presence of bone metastases negatively affected survival (HR 2.53, 95% CI 1.05-6.09; P = 0.04). CONCLUSIONS Treatment with curative intent of selected oligometastatic NSCLC, including resection of the primary tumour, can be performed safely and with excellent 5-year survival rates, especially in younger patients with pN0 disease.

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PROGNOSTIC FACTORS OF OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER FOLLOWING RADICAL THERAPY: A MULTICENTER-ANALYSIS

I. Opitz[1], M. Patella[1], L. Payrard[2], J.Y. Perentes[2], R. Inderbitzi[3], H. Gelpke[4], S. Schulte[4], M. Diezi[1], M. Gonzalez[2], T. Krueger[2], W. Weder[1]

[1]Department of Thoracic Surgery, University Hospital of Zurich, Zurich, Switzerland

[2]Department of Thoracic Surgery, University Hospital of Vaudois, Lausanne, Switzerland

[3]Department of Thoracic Surgery, San Giovanni Hospital, Bellinzona, Switzerland

[4]Department of Thoracic and Visceral Surgery, Cantonal Hospital, Winterthur, Switzerland

I. Opitz and M. Patella equally contributed to the study as first co-authors

T. Krueger and W. Weder equally contributed to the study as last co-authors

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Visual abstract:

- What are the prognosis and prognostic factors of patients with oligometastatic NSCLC treated with curative intent?
- 5 year-overall survival was 36% for all and 83% for patients <60 and pN0, bone metastases have a negative impact
- Resection of primary NSCLC and radical treatment of metastasis is safe and effective in selected patients, nodal staging appears mandatory

Corresponding author:

Isabelle Opitz, MD, FEBTS

Department of Thoracic Surgery, University Hospital Zurich,

Rämistrasse 100, 8091 Zürich, Switzerland

+41442558802

isabelle.schmitt-opitz@usz.ch

ABSTARCT

Objectives

Patients with oligometastatic non-small cell lung cancer (NSCLC) may benefit from therapy with curative intent. We aimed to identify prognostic factors related to better prognosis, in a multicenter analysis of patients who underwent surgery of primary tumors, in combination with radical treatment of all metastatic sites.

Methods

We retrospectively reviewed the records of oligometastatic patients who underwent resection of primary tumor at four centers, (08/2001-02/2018). Oligometastasis was defined as ≤5 synchronous metastases in ≤2 organs. Radical metastatic treatment was surgery, radiotherapy or a combination. Cox proportional hazards model was used for identification of prognostic factors on overall survival (OS).

Results

We treated 124 patients; 72 (58%) were male, mean age 60±9.8 years, with 87 (70%) adenocarcinoma. Sixty-seven (54%) had pathological positive nodal status (pN). Brain metastasis was most common (n=76; 61%) followed by adrenal (n=13;10%) and bone (n=12;10%). Systemic therapy was administered in 101 (82%) patients. Median follow-up was 60 months (95% CI: 41, 86).

Thirty- and 90-day mortality were 0 and 2.4% respectively. One-, 2-, and 5-year OS was 80%, 58%, and 36% respectively. Cox regression analysis showed that patients ≤60 years (HR: 0.41, 95% CI: 0.24, 0.69, p=0.001) and patients with pN0 (HR 0.38, 95% CI: 0.21, 0.69, p=0.002) had a significant survival benefit. The presence of bone metastasis negatively affected survival (HR: 2.53, 95% CI: 1.05, 6.09, p=0.04).

Conclusions

Treatment with curative intent of selected oligometastatic NSCLC, including resection of the primary tumor, can be performed safely and with excellent 5-year survival, especially in younger patients with pN0 disease.

Key words: oligometastatic NSCLC, surgery, metastasis, radical treatment, prognostic factors

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide with poor survival for the metastatic stage. However, since Hellman and Weichselbaum described the concept of oligometastatic state in 1995(1), the interest in the heterogeneity of stage IV non-small cell lung cancer (NSCLC) has exponentially grown within the scientific community. Current European(2) and American(3) guidelines indicate local ablative treatment for primaries and metastatic site in selected patients. However, the evidence mostly results from case-series and is therefore considered low grade. Two prospective trials lead by radio-oncologists(4,5) reported a significant improved progression-free survival (PFS) and overall survival (OS) with the use of local therapies to all disease sites. Surgery has been part of the treatment strategy in a small percentage of patients in one trial(4), while the other only focused on the use of stereotactic body radiotherapy (SBRT). Nevertheless, surgery has been used in oligometastatic NSCLC for more than 40 years, with a broad range of results(6).

According to the Swiss Cancer Report 2015(7), in Switzerland lung cancer accounts for 11.8% of all types of cancer among men and for 8.5% among women. Between 2008 and 2012 an average of some 2500 men and 1500 women were diagnosed with lung cancer each year. Median age at diagnosis is 70 year for man and 69 for woman, with an incidence rate that rise up between 75 and 79 year, then decline.

In this study, we analyzed the long-term experience of four SWISS surgical centers with the aim to identify prognostic factors associated with better outcome for patients with oligometastatic disease treated with curative intent.

PATIENTS AND METHODS

Patients' institutional databases of four surgical centers in Switzerland (Universitätsspital Zürich, Ospedale Regionale di Bellinzona e Valli, Centre Hospitalier Universitaire Vaudois of Lausanne, Kantonsspital Winterthur) were screened for patients treated for metastatic NSCLC between 2001 and 2018. The centers included are two university hospitals and two cantonal hospitals, accounting

for the larger number of lung cancer patients/year visited in each canton(8). Local ethics committees approved the study (2019-00636), written consent was obtained from living patients and waived for the deceased ones. We included patients who fulfilled the following criteria: age ≥ 18 years; histologically confirmed NSCLC with ≤ 5 synchronous metastasis in ≤ 2 organs; radical surgical treatment of the primary tumor ± neoadjuvant/adjuvant therapy; radical treatment of all metastatic sites. For metastasis treated with radiotherapy, morphological/metabolic criteria were used to confirm complete response, for brain metastasis, the radicality was confirmed by neuro-radiologist based on MRI imaging. Surgical resections performed with palliative or diagnostic intent were excluded. All patients were discussed in multidisciplinary tumor boards for the indication of surgical and-or adjuvant as well as the therapy sequence.

We included a small cohort (21 cases) of patients described previously(9). Patients were uniformly re-staged according to the American Joint Committee on Cancer (AJCC) 7th edition; therefore, we excluded from the previous series the cases with synchronous nodules in same lung within different lobes. Patients with incomplete data about surgical indication, intent of treatment and patients who did not complete the radical management were excluded from the analysis.

Primary end point of the study was overall survival (OS) defined as the time from the first treatment (lung surgery, metastasis ablation or neoadjuvant treatment) to the date of death, with living patients censored at the date of last follow-up. Secondary end point was the progression-free survival (PFS) defined as the time from the first treatment to the date of first progression, local or distant. Follow-up information were obtained from electronic records or, if absent, from telephonic interviews with patients and relatives.

The following variables were collected and considered for analysis: gender, age (≤ 60 vs > 60 years), , pathological T-stage (pT1-2 vs 3-4), pathological N-stage (pN0 vs 1-2 and pN0-1 vs 2), metastasis location (brain vs other, adrenal vs other, bone vs other, lung vs other), number of metastasis (single vs multiple), single vs multiple organs involved, neoadjuvant and adjuvant therapy, resection margins (R0 vs R+), metastasis treatment (surgery vs no surgery, combined treatment vs single strategy), timing of treatment (metastasis first vs primary first).

Median OS and PFS were estimated by the Kaplan–Meier method. Differences in survival rates were described by median OS, hazard ratio (HR) and 95% confidence intervals (CIs) and compared by the log-rank test. Predictors' selection was based on clinical knowledge, the Cox regression model was assessed for multivariable survival analyses. Backward elimination was performed with a p-value criterion of 0.15. P-values were considered significant below 0.05. To avoid bias related to collinearity, highly correlated variables were tested separately and the Akaike information criterion (AIC) was used to estimate the relative quality of the models, selecting the ones with best goodness of fit. Data processing and analysis were performed with the statistical software system Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

Clinical characteristics

Between August 2001 and February 2018, 124 patients were included for analysis. This population accounted for the 3-7% of all anatomical lung resections performed in the different centers. Seventy-two patients (58.1%) were males, mean age was 60 (SD:9.8) years. Adenocarcinoma was the most common histology, identified in 87 patients (70.2%), followed by squamous-cell carcinoma in 18 (14.5%) and large-cell carcinoma in 8 (6.4%). Molecular analysis were performed routinely after 2012 and in 20% of patients, some driver mutations were found (EGFR, ALK; KRAS mutation, PDL-1 overexpression, rare mutations). The majority of patients (74%) had advanced intra-thoracic disease (T and N parameters). Fifty-six patients (45.2%) were N0 at pathological examination, while 23 (18.5%) and 44 (35.5%) had pN1 and pN2, respectively. Seventy-six (61.3%) had brain metastasis, which was the most common site, while 13 patients (10.4%) had adrenal metastasis, 12 (9.7%) had bone localizations and 8 (6.3%) had contralateral lung nodules. All lung metastasis were single contralateral nodules. The diagnosis of synchronous metastasis was formulated based on pathology (morphology and mutational status when available) after resection in all of them but one (diagnosis based on CT morphology and treated with radiotherapy).Overall, 96 patients (77.4%) had a single metastasis and the vast majority 97.6% had a single organ involved. Only 3 patients had two organs involved by metastasis.

Regarding the pre-operative staging, all patients underwent PET scan and 36% underwent invasive mediastinal staging (either EBUS or mediastinoscopy) based on imaging results.

Treatment variables

Thirty-seven patients received neo-adjuvant therapies, in 57 patients initial treatment was on the metastatic sites, 30 patients underwent lung resection as first. The median interval between the treatment of the primary tumor and the metastatic sites was 39 day (Interquartile Range: 63 days) in both cases (metastasis first vs primary first). Treatment of the primary tumor was surgery for all patients, including lobectomies (n=90), pneumonectomies (n=11), segmentectomies (n=11) and extended resections (n=12). Radical mediastinal lymphadenectomy was performed in all patients with one exception. Minimally invasive approach (VATS) was used in 27 patients (22%) for resection of the primary tumor and in all the 7 patients in whom the lung metastasis were treated with surgery. There was no in-hospital mortality and the 90-day mortality was 2.4%. Clear resection margins (R0) were obtained in 108 cases (88.5%). Thirty-seven patients (29.9%) received neo-adjuvant treatment in form of chemotherapy (35, 28.8%) or chemo-radiotherapy (2, 1.6%). General recommendation for advanced intrathoracic stages included bimodal (surgery/chemotherapy) or trimodal treatments (surgery/chemotherapy/radiotherapy).

Metastases were treated with surgical resection in 46 cases (37.1%), with radiotherapy in 35 (28.2%) and with a combination of both in 42 patients (35%). One patient had a liver metastasis treated with radiofrequency ablation.

Sixty-four (51.6%) patients received adjuvant treatments with different combinations including immunotherapy in 14 cases. With regards of chemotherapy, used alone or in combination with radiotherapy, or immunotherapy in 46 patients, the most common scheme included a platinum agent used with doublets or triple-drug regimens. Population and treatments characteristics are expressed in Table 1.

Overall survival results

Median follow-up time calculated with reverse Kaplan-Meyer was 60 months (95% confidence interval (CI): 41, 86). OS at 1-, 2-, 3- and 5-years was 80%, 58%, 49% and 36% respectively (Figure 1A).

Cox regression analysis showed that age ≤60 years, nodal status and bone locations for metastasis significantly influenced the survival. To avoid collinearity, two separate Cox regression models were calculated for pN0 status vs pN1-2 and for pN0-1 vs pN2. In both cases, all the tested variables remained statistically significant, but the AIC analysis showed a better goodness of fit of the first model (370 vs 377). Therefore, the final model showed that age ≤60 years (HR: 0.41, 95% CI: 0.24, 0.69, p=0.001) and negative pathological mediastinal lymph node status (HR: 0.38, 95% CI: 0.21, 0.69, p=0.002) remained strongly associated with good prognosis. The presence of bone metastasis negatively affected survival in the same model (HR: 2.53, 95% CI: 1.05, 6.09, p=0.04). Results are expressed in Tables 2 and 3. Figure 2 represents the survival curves according to nodal status.

Progression-free survival results

Median PFS time was 11 months (95% CI: 8, 13). PFS survival at 1-, 2-, 3- and 5-years was 41%, 29%, 25% and 23%, respectively. Two Cox models were constructed including separately pN0 vs 1-2 and pN1-2 vs N0. The Cox regression analysis indicated that negative nodal status (HR: 0.38, 95% CI: 0.41, 0.10, p<0.001) and the presence of bone metastasis (HR: 1.88, 95% CI: 1.06, 3.34, p=0.03) remained independently associated with the outcome. The model including the groups pN0-1 vs 2 showed to have worst goodness of fit compared with the one displaced (AIC: 508 vs 514). Results of the analysis are expressed in Tables 4 and 5.

Subgroup analysis

During the follow-up time, 92 patients (74.1%) experienced a recurrence. Only 8 recurrences (8.7%) were pure loco-regional (lung and/or mediastinal lymph nodes). Most of the patients (84, 68%) had distant recurrence with or without lung recurrence.

Seventy-nine patients received further treatments, either local and/or systemic after the first progression.

Within our population with age ≤60 years and nodal status pN0, we counted 28 patients. OS at 1- and 5-year were 100% and 83% respectively (Figure 1B). Twenty patients had brain metastasis (71.4%) while only one had a bone localization. One patient had a single pleural lesion, 4 had adrenal metastasis and 2 had lung nodules. In 21 cases (75%) the metastatic site was treated with surgery with (10 patients) or without the use of radiotherapy boost on the surgical field. Fourteen patients (50%) experienced a recurrence during the follow-up. Median PFS was 40 months (range: 8-137 months). All patients had further treatments after first progression.

DISCUSSION

Our results support aggressive surgical treatment of oligometastatic NSCLC in a context of curative strategies with 5 year OS of 35% for all, and 83% for younger patients in absence of lymph node involvement.

The literature on treatment of stage IV lung cancer is heterogeneous, with inconsistent definitions of "oligometastatic" status, type of treatment administered, populations included and outcome description. In a systematic review published in 2013(10), aiming to define the oligometastatic state of NSCLC, the reported 5-year OS for patients treated with curative intent was ranging from 8.3% to 86%. However, even with such a wide range of prognosis, the control of the primary tumor was considered highly influencing the survival. A study designed as propensity score analysis comparing 180 patients with synchronous single organ metastasis who received local ablative treatment of all disease sites versus palliative treatment(11), showed a median OS of 60 months in the first group and a 22.5 months OS in the control group.

As regards the best treatment for primaries, large epidemiological databases analyses have been recently published. The first one(12), based on data extracted from the National Cancer Database, considered a population of over 3.000 patients who underwent lung resection for stage IV NSCLC. It reported a 5-year OS of 21.1%, recommending surgical resection for tumors staged T1-2,N0-1,M1 or T3,N0,M1. The second large population-based study was based on the Surveillance, Epidemiology and End Results database(13). This retrospective analysis was conducted on over 39.000 cases of stage IV

NSCLC, of which 1206 underwent surgical resection of primary tumor. The authors found that primary tumor resection was associated with significantly longer OS in different cohorts of patients. Other clinical and epidemiological studies, favored surgery for the primary site as cornerstone treatment of oligometastatic NSCLC(14-17).

We focused our analysis on patients undergoing lung resection and local radical treatment for metastatic sites. Overall, our population was younger than the average of NSCLC patients, and, possibly in good clinical conditions, particularly, the best results in terms of survival have been obtained in younger patients (≤60 years). Indication for anatomical lung resections is usually discussed in multidisciplinary settings, and operability criteria, such as respiratory reserve and cardiac risk are part of the decision-making process. In our cohort, we did not have information on performance status, but we can assume that, as surgical candidates, it was less than 2 in all patients.

Other studies reported that age and performance status influence the prognosis. Ampil(18), in a series of 72 cases, found that patients with solitary metastasis younger than 65 years had a longer survival compared to the older counterpart. It is intuitive, that patients in better general conditions are more prone to be included in aggressive treatment programs. As an example, the study of Frost(11), analyzed 107 patients who received local ablative treatments for synchronous single organ metastatic lung cancer, comparing them with 266 patients who did receive palliative treatments. Good performance status was strongly associated with better survival within the control group and remained associated with good outcome after propensity score matching of groups. In our series, age ≤60 years correlated with OS but not with PFS: these results, along with the published literature, generally indicate that patients in good clinical conditions could possibly be selected for upfront aggressive treatments and for further therapies after first progression.

The other factor strongly associated with OS and PFS in our study was the negative nodal status of the primary tumor. These results are in line with most published reports, either from clinical series and analysis of epidemiological databases(10,11,15,19,22). A large patient data meta-analysis(20) identified a subgroup of patients classified as “intermediate” risk with synchronous metastasis and negative nodes. Those patients exhibited a 5-year OS of 36.2% in the training set and 29.2% in the validation set, while patients considered as “high risk”, with synchronous metastasis and N≥ 1, had a 5-

year OS of 13.8%. These results are superimposable with our own data. The 2018 European Society for Medical Oncology(2) guidelines also mention these groups definition. The National Comprehensive Cancer Network guidelines(3) suggest that in patients who have single brain or adrenal metastases, and a primary tumor that is T1-2/N0-1 or T3/N0, the management should include local treatment of the metastasis followed by resection of the lung lesion, in combination with chemotherapy either before or after lung resection. The National Cancer Database analysis performed by Yang(12), supporting these assertions, showed a 5-year OS of 28.8% for stages T1-2/N0, 20.5% for stage T3-4/N0 and 17.4 for stage T1-2/N1, leading to some conflicting interpretations.

Possibly, the difference in survival between N0 and N-positive patients reflects the parallel patterns of tumor spread through hematogenous and lymphatic pathways, which can affect the results in terms of local thoracic disease control.

Although the median OS in our series was 36 months, a proportion of patients progressed locally or distantly after treatment with a median PFS of 11 months. The factors negatively associated with progression were nodal involvement and presence of bone metastasis.

In our subgroup ≤60 years and N0, the 5-year OS was 83%. This result does not translate in a curative treatment for all patients. Indeed, 50% of patients experienced a recurrence, with a median PFS time of 40 months, with a consistent difference with the overall population, who had a median PFS time of 11 months. This introduces the concept of possible identification of indolent disease, rather than truly eradicated cancers. Again, the young age of the patients might have conditioned the proposal and acceptance of further treatments after first progression, which has been 100% in all recurrent cases in our best sub-group. In general, the majority of patients received additional therapies for recurrent disease with redo surgery for brain metastasis, radiation therapy, chemotherapy or target/immunotherpies. These data, along with the difference between the OS and the PFS, indicates that good candidates might benefit from aggressive treatments and “rescue” therapies in selected cases. New alternative strategies as ultraguided ablative techniques may further improve the outcome.

Because of the design of our study, based on a surgical population, we can draw two considerations: we did not include any N3 patient who did not candidate for lung resection, and our

analysis considered the pathological staging. The latter point might be a limit of the study, as it does not offer pre-treatment indications, which are mandatory in the real world. On the other hand, results are adherent with the true stage of the disease. Based on this assumption, we strongly recommend invasive nodal staging for all patients considered for lung resection of oligometastatic NSCLC. Another limit of our study is its retrospective design. Including patients treated more than a decade ago allowed a long follow-up, but included heterogeneous surgical and oncological therapies. Immunotherapy was administered to few patients, possibly biasing its impact on the prognosis of these patients knowing to benefit from it. Moreover, a long follow-up offers a good overview on patients' survival, but introduces a bias due to deaths not related to cancer diagnosis. In fact, usual lung cancer patients are life-longing smokers and present many comorbidities. Our population has a selection-bias compared to the general patients with stage IV NSCLC, and without a control group, it is difficult to ascertain whether the treatment solely, rather than patient selection, has led to positive outcome. Being a surgical population, some patients' characteristics are not truly representative of the general stage IV patients. As an example, the mean age of our cohort is quite low, the performance status and the general clinical conditions must have been high and the burden of disease was surely low. All these considerations must be taken into account when looking at the results. Indeed, our results may reflect an "improved selection of winners": the baseline characteristics of the patients justified the choice of aggressive treatments at first glance and also the use of further treatments after first progression. Selection bias can be noted also in the number of metastasis and metastatic organs (77.4% had a single metastasis and 97.6% had a single organ involved). Overall, the number of the patients is limited and, even though the results are interesting, careful interpretation is mandatory specifically for the subgroup analysis.

Considering the limitations, some conclusions can be made. Surgery for primary lung cancer in oligometastatic stage IV is confirmed to offer a good prognosis with low morbidity and mortality in selected patients. The presence of lymph-node involvement confirms to influence both the OS and the PFS therefore, the candidate selection process should include accurate staging. Even if strong conclusions cannot be drawn from a retrospective analysis of less than 200 cases, the encouraging results might help in the decision-making process during multidisciplinary discussion and patients counselling. It is worth to investigate further prognostic factors, possibly including genetics and biomarkers that

might refine clinical indicators for patient selection and that might help to identify NSCLCs with different clinical and biological behavior. Finally, it is notable that even in case of nodal involvement, the results showed in our series are acceptable. In the era of immuno- and target-therapies, this might open to synergic strategies including surgery, in order to reduce the mutational tumor burden, even in more advanced cases.

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Figure 1: Survival curves for the entire population (A) and for patients ≤60 years and N0 (B). Median OS starting from primary tumor resection was 34 months (95% CI: 22-51)

Figure 2: Survival curves for patients with N0 vs N1-2

311 **Table 1:** Population and treatments characteristics

Population	124
GENERAL VARIABLES	
Male gender	72 (58.1%)
Age (mean, SD)	60 , 9.8
Histology	
Adenocarcinoma	87 (70.2%)
Squamous Cell Carcinoma	18 (14.5%)
Large Cell Carcinoma	8 (6.4%)
Neuroendocrine	3 (2.4%)
Other	8 (6.4%)
PRIMARY VARIABLES	
T-descriptor (UICC VII)	
pTx	2 (1.6%)
pT1	22 (17.7%)
pT2	53 (42.7%)
pT3	37 (29.8%)
pT4	10 (8.1%)
N-descriptor	
pNx	1 (1%)
pN0	56 (45.2%)
pN1	23 (18.5%)
pN2	44 (35.5%)
METASTASIS VARIABLES	
Mets location	
Brain	76 (61.3%)
Adrenal	13 (10.4%)
Bone	12 (9.7%)
Lung	8 (6.3%)
Other	12 (9.6%)
Multiple locations	3 (2.4%)
Single metastasis	96 (77.4%)
Single organ involved	121 (97.6%)
TREATMENT VARIABLES	
Neoadjuvant	37 (29.9%)
CHT	35 (28.2%)
CHT/RT	2 (1.6%)
Treatment for primary	
Surgery	124 (100%)
R0 (surgical margins primary)	108 (88.5%)
30-day mortality	0
Treatment for mets	
Surgery	46 (37.1%)
RT	35 (28.2%)
Combined	42 (35%)
Other	1 (1%)
Adjuvant	64 (51.6%)
CHT	40 (32.2%)
CHT/RT	2 (1.6%)

Immunotherapy	7 (5.6%)
CHT/immunothearpy	3 (2.4%)
RT	8 (6.4%)
RT/immunotherapy	6 (4.8%)
Immunotherapy/RT/CHT	1 (1%)
RECURRENCE	92 (74.1%)
Type of recurrence	
Loco-regional (lung and lymph-nodes)	8 (8.7%)
Local mets recurrence	35 (38%)
Treatment of recurrence	78 (84.8%)
Treatment with curative intent	11 (12%)
Type of treatment	
Surgery	15 (16.3%)
RT	22 (23.9%)
CHT	9 (9.8%)
Immunotherapy	12 (14.1%)
Combined	20 (21.7%)

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Table 2: Results of Cox regression analysis for overall survival

Variable	HR	95% CI	p-value
Age ≤ 60 vs >60	0.41	0.24, 0.69	0.001
pN0 vs 1-2	0.38	0.21, 0.69	0.002
Mets location			
Bone vs other	2.53	1.05, 6.09	0.04
Lung vs other	0.18	0.02, 1.45	0.1

317 **Table 3:** Overall survival at 2 and 5 years according to significant predictors

Variable (grouped)	Median	Survival function at 2 years	CI (2 years)	Survival function at 5 years	CI (5 years)	Log-rank
pN0	78	76	0.61, 0.84	61	0.45, 0.75	<0.001
pN1-2	20	44	0.31, 0.56	16	0.07, 0.29	
Age ≤60 y	54	69	0.55, 0.80	45	0.29, 0.59	0.002
Age >60 y	22	46	0.33, 0.59	27	0.14, 0.41	
Bone mets	12	16	0.01, 0.49	NR	-	<0.001
Other sites	39	61	0.51, 0.70	39	0.29, 0.50	

318 NR: not reached

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320 **Table 4:** Results of Cox regression analysis for progression-free survival

Variable	HR	95% CI	p-value
Metastasis first	0.59	0.34, 1.04	0.09
pN0 vs 1-2	0.38	0.41, 0.10	<0.001
Mets location			
Bone vs other	1.88	1.06, 3.34	0.03
Brain vs other	2.02	0.87, 4.74	0.1

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Table 5: Progression-free survival at 2 and 5 years according to significant predictors

Variable (grouped)	Median	Survival function at 2 years	CI (2 years)	Survival function at 5 years	CI (5 years)	Log-rank
pN0	24	48	0.34, 0.62	37	0.23, 0.52	<0.001
pN1-2	8	15	0.07, 0.25	11	0.04, 0.22	
Bone mets	3	NR	-	NR	-	0.03
Other sites	11	31	0.23, 0.40	24	0.16, 0.33	

NR: not reached

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